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SCIENTIFIC ARTICLE

Administration of paracetamol versus dipyrone by intravenous patient-controlled analgesia for postoperative pain relief in children after tonsillectomy[☆]

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Abstract

Background and objective: We compared the efficacy of intravenous (IV) paracetamol versus dipyrone via patient-controlled analgesia (PCA) for postoperative pain relief in children.

Methods: The study was composed of 120 children who had undergone elective tonsillectomy after receiving general anesthesia. Patients were divided into 3 groups according to the dosage of postoperative intravenous-patient-controlled analgesia: paracetamol, dipyrone, or placebo. Pain was evaluated using a 0- to 100-mm visual analog scale and 1- to 4-pain relief score at 30 min, 1, 2, 4, 6, 12, and 24 h postoperatively. Pethidine (0.25 mg kg⁻¹) was administered intravenously to patients requiring rescue analgesia. Pethidine requirements were recorded during the first 24 h postoperatively, and treatment related adverse effects were noted.

Results: Postoperative visual analog scale scores were significantly lower with paracetamol group compared with placebo group at 6 h ($p < 0.05$), dipyrone group compared with placebo group at 30 min and 6 h ($p < 0.05$). No significant differences regarding visual analog scale values at 1, 2, 4, 12, and 24 h were found. No significant differences were found between groups with respect to pain relief score ($p > 0.05$). Postoperative pethidine requirements were significantly lower with paracetamol and dipyrone groups compared with placebo group (62.5%, 68.4% vs 90%, $p < 0.05$). No significant differences were found between groups with respect to nausea, vomiting and the any other adverse effects of the drugs ($p > 0.05$).

Conclusions: Paracetamol and dipyrone have well tolerability profile and effective analgesic properties when administered IV-PCA for postoperative analgesia in children after tonsillectomy.

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PALAVRAS-CHAVE

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Pós-operatório;
Tonsilectomia

Administração de paracetamol *versus* dipirone em analgesia controlada pelo paciente por via intravenosa para alívio da dor no pós-operatório de crianças após tonsilectomia**Resumo**

Justificativa e objetivo: Comparamos a eficácia da administração de paracetamol *versus* dipirone em analgesia controlada pelo paciente (PCA) por via intravenosa (IV) para alívio da dor no período pós-operatório em crianças.

Métodos: O estudo foi composto por 120 crianças submetidas à tonsilectomia sob anestesia geral. Os pacientes foram divididos em três grupos de acordo com a dose IV de analgesia controlada pelo paciente no pós-operatório: paracetamol, dipirone ou placebo. A dor foi avaliada usando uma escala visual analógica de 0-100 mm e escore de 1-4 para alívio da dor nos tempos de 30 minutos, 1, 2, 4, 6, 12 e 24 horas de pós-operatório. Petidina ($0,25 \text{ mg kg}^{-1}$) foi administrada IV aos pacientes que precisaram de analgesia de resgate. A necessidade de petidina foi registrada durante as primeiras 24 h de pós-operatório, e os efeitos adversos relacionados ao tratamento foram registrados.

Resultados: Os escores da escala visual analógica no pós-operatório foram significativamente menores no grupo paracetamol em comparação com o grupo placebo em 6 h ($p < 0,05$), no grupo dipirone em comparação com o grupo placebo em 30 min e 6 h ($p < 0,05$). Não houve diferença significativa em relação aos valores da escala visual analógica nos tempos avaliados de 1, 2, 4, 12 e 24 horas. Não houve diferença significativa entre os grupos quanto ao escore de alívio da dor ($p > 0,05$). A necessidade de petidina foi significativamente menor nos grupos paracetamol e dipirone em comparação com o grupo placebo (62,5%, 68,4% vs. 90%, $p < 0,05$). Não houve diferença significativa entre os grupos em relação à incidência de náusea, vômito e outros efeitos adversos dos medicamentos ($p > 0,05$).

Conclusões: Paracetamol e dipirone possuem um perfil de boa tolerabilidade e propriedades analgésicas eficazes quando administrados IV para PCA no pós-operatório de crianças após tonsilectomia.

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Introduction

Tonsillectomy can be considered as the most widely practiced one among the childhood surgical operations. Sufficient treatment of postoperative pain in children is a main concern for patients, parents and clinicians.¹ However, successful treatment of postoperative pain in children is still difficult despite of recent progress in control technique of pain and analgesics. Insufficient postoperative pain control can result in impairment of the feature of life, recovery of patients and social stress for both the children and the parents.¹ Analgesics such as opioids and non-opioids are frequently used for postoperative pain management. The severity of side effects related with effective opioid dosage may restrict their usage for sufficient postoperative pain control. Intravenous (IV) non-opioid analgesics are used extensively for the treatment of postoperative pain. Non-opioid analgesics have been shown to effectively decrease postoperative pain, opioid consumption and thus their adverse effects during the postoperative period in children.² There are only a few alternative analgesic agents for IV non-opioid analgesia for the treatment of postoperative pain in pediatric patient.² Paracetamol (acetaminophen)²⁻⁶ and dipyrone (metamizol)⁷⁻⁹ are two frequently used IV non-opioid analgesics.^{10,11} Paracetamol is the most popular, effective and most widely used non-opioid analgesic for acute pain.¹¹ Dipyrone has potent pain-relieving, antipyretic, spasmolytic properties, and is

also an effective non-opioid analgesic for acute pain.¹¹ Paracetamol and dipyrone generally show similar clinical efficacy.^{5,12} On the other hand, administration of paracetamol resulted in a significant reduction in the number of patients requiring opioid analgesics to achieve adequate postoperative pain relief when compared with dipyrone.¹³ IV-PCA is an effective method for the treatment of postoperative pain both in adults and children.² IV-PCA is an effective and safe method providing appropriate levels of analgesia in children over 5 years of age.^{14,15} The literature review reveals that there are a few studies conducted with non-opioid analgesics by IV-PCA for treatment of postoperative pain in only adults.¹⁶⁻²¹ Although non-opioid analgesics (paracetamol and dipyrone) are widely used in the pediatric age group, surprisingly we have not seen any report concerning non-opioid analgesic (paracetamol or dipyrone) use via IV-PCA for postoperative pain treatment in children.

In our study, we aimed to test the hypothesis that IV-PCA with paracetamol for treatment of postoperative pain in children after tonsillectomy is superior and an acceptable alternative for dipyrone by IV-PCA in terms of an adequate postoperative pain relief and reduction in the number of patients requiring opioid analgesics.

Methods

The protocol was approved by the Ethics Committee of University Faculty of Medicine (project no: KA08/47).

Written informed parental consent and verbal child assent were obtained from 143 ASA I patients (according to the American Society of Anesthesiologists Physical Status Classification system; aged 7–15 years) who had been scheduled for elective tonsillectomy. The study was a prospective, randomized, placebo-controlled double-blind study. Patients were instructed how to use a PCA pump prior to surgery and were informed about the data to be collected postoperatively using a visual analog scale (VAS) and pain relief score (PRS). Exclusion criteria included a history of significant hepatic, pulmonary, renal, or cardiac disease; hypersensitivity to the study medications; any disorder contraindicating administration of non-opioid analgesics; peptic ulcer disease; asthma; a bleeding disorder; concomitant medication (anticonvulsants, corticosteroids, psycho tropics, or antihistamines); intolerance to non-opioids. Those unable to understand the instructions regarding the use of PCA were not included in the study. Patients were not allowed to receive any analgesics 24 h prior to the operation. Patients were assigned randomly to 1 of 3 study groups, according to a pre-generated randomization scheme created by the web site Randomization.com (<http://www.randomization.com>), to receive IV-PCA treatment with paracetamol, dipyrone, or placebo (0.9% NaCl).

The analgesic solution (500 mL 0.9% NaCl) was prepared by one of the researchers (AK) blinded to the treatment protocol and not involved in the intraoperative and postoperative patient treatment. Patients were blind to the treatment. Postoperative data were collected by another anesthesiologist (EC) blinded as to which analgesic was used. The solutions contained either 2 mg mL⁻¹ paracetamol, 2 mg mL⁻¹ dipyrone, or 1 mL normal saline. No premedication was given to the children. General anesthesia was induced with thiopental (5–7 mg kg⁻¹), fentanyl (1 µg kg⁻¹), and vecuronium (0.1 mg kg⁻¹). After tracheal intubation, mechanical ventilation was initiated, and a 50% mixture of N₂O/O₂ was administered throughout the surgery. Anesthesia was maintained with isoflurane 1.2 MAC. Residual muscle relaxation was reversed with neostigmine and atropine at the end of the operation. All patients were extubated in the operating room. Patients were assigned to one of the following 3 groups with respect to the analgesic agent administered via IV-PCA (Abbott Pain Management Provider, Abbott Laboratories, Abbott Park, Ill, USA) in the recovery room:

Paracetamol: Loading dose of 4.5 mg kg⁻¹ IV, followed by 0.5 mg kg⁻¹ h⁻¹ basal infusion, 1 mg kg⁻¹ bolus dose, lock-out time 30 min for 24 h (total dose of paracetamol was limited to 10 mg kg⁻¹ 4 h⁻¹).

Dipyrone: Loading dose of 4.5 mg kg⁻¹ IV, followed by 0.5 mg kg⁻¹ h⁻¹ basal infusion, 1 mg kg⁻¹ bolus dose, lock-out time 30 min for 24 h (total dose of dipyrone was limited to 10 mg kg⁻¹ 4 h⁻¹).

Placebo: Loading dose of 2 mL kg⁻¹ IV, followed by 0.5 mL kg⁻¹ h⁻¹ basal infusion, 1 mL kg⁻¹ bolus dose, lock-out time 30 min.

Postoperative pain intensity was evaluated by the patient according to a 0- to 100-mm horizontal VAS at 30 min, 1, 2, 4, 6, 12, and 24 h postoperatively. PRS (Pain Relief Score) was

evaluated by the patient according to a 0 = none, 1 = little, 2 = some, 3 = a lot, and 4 = complete relief at 30 min, 1, 2, 4, 6, 12, and 24 h postoperatively. Pethidine (0.25 mg kg⁻¹) was given IV to patients whose VAS score was ≥ 40 mm and/or PRS was < 2 and then recorded (total dose of pethidine was limited to 1.5 mg kg⁻¹ 6 h⁻¹). Adverse effects including nausea, vomiting, bleeding at the surgical field, dyspepsia, allergic reactions, and use of antiemetic medication (metoclopramide HCl) also were recorded during the first 24 h postoperatively.

A power analysis was performed based on the total pethidine requirement data obtained from the first 15 patients in the placebo group. The results of the first 15 patients in the placebo group showed that mean total pethidine requirement was 0.81 ± 0.39 mg kg⁻¹ during the first 24 h postoperatively. If we also assumed a two-tailed type I error of 0.05 and a power of 0.80, approximately 40 patients in each group were required in order to detect a 30% reduction in the dose of total pethidine requirement between the groups. Analysis was performed by Power and Precision V4 TM (version 4.1.0, Biostat Inc., Englewood, NJ) statistical program.

All statistical calculations were performed using SPSS for Windows software (Statistical Package for the Social Sciences, version 11.0, SSPS Inc, Chicago, IL, USA). Differences between the 3 groups were analyzed using an analysis of variance (ANOVA) test or its nonparametric counterpart, the Kruskal–Wallis test. Post hoc analysis was performed using the Bonferroni test. Homogeneity of variances was calculated using Levene's test and Lilliefors significance correction. Chi-square or Fisher's exact tests were used to analyze categorical variables where appropriate. Data are expressed as means ± SD. Differences were considered statistically significant at levels of $p < 0.05$.

Results

One hundred and forty three children were screened to participate in this study. During screening 8 patients were found to be not eligible for the study, 9 patients' parents declined to give consent and 6 patients were excluded due to other reasons. Finally, a total of 120 patients constituted the study population (Fig. 1). The demographic characteristics and operation time of the groups were found similar (Table 1). VAS values for the dipyrone group (39.8 ± 31.9 mm) were significantly lower than those of the placebo group (56.6 ± 27.2 mm) at 30 min postoperatively ($p = 0.044$). VAS values for the paracetamol group (17.5 ± 15.8 mm) and dipyrone group (20.9 ± 22.4 mm) were significantly lower than those of the placebo group (30.1 ± 23.3 mm) at 6 h postoperatively (paracetamol versus placebo; $p = 0.013$, dipyrone versus placebo; $p = 0.045$). No statistically significant differences were found between the groups in terms of VAS values 1, 2, 4, 12, and 24 h postoperatively ($p > 0.05$ at each time point, Table 2). No statistically significant differences were found between the groups in terms of PRS values 30 min, 1, 2, 4, 6, 12, and 24 h postoperatively ($p > 0.05$ at each time point, Fig. 2). No statistically significant difference was found in the cumulative amounts of non-opioid analgesics consumed by the patients (paracetamol 955.1 ± 497.8 mg and dipyrone 832.1 ± 375.9 mg, $p > 0.05$).

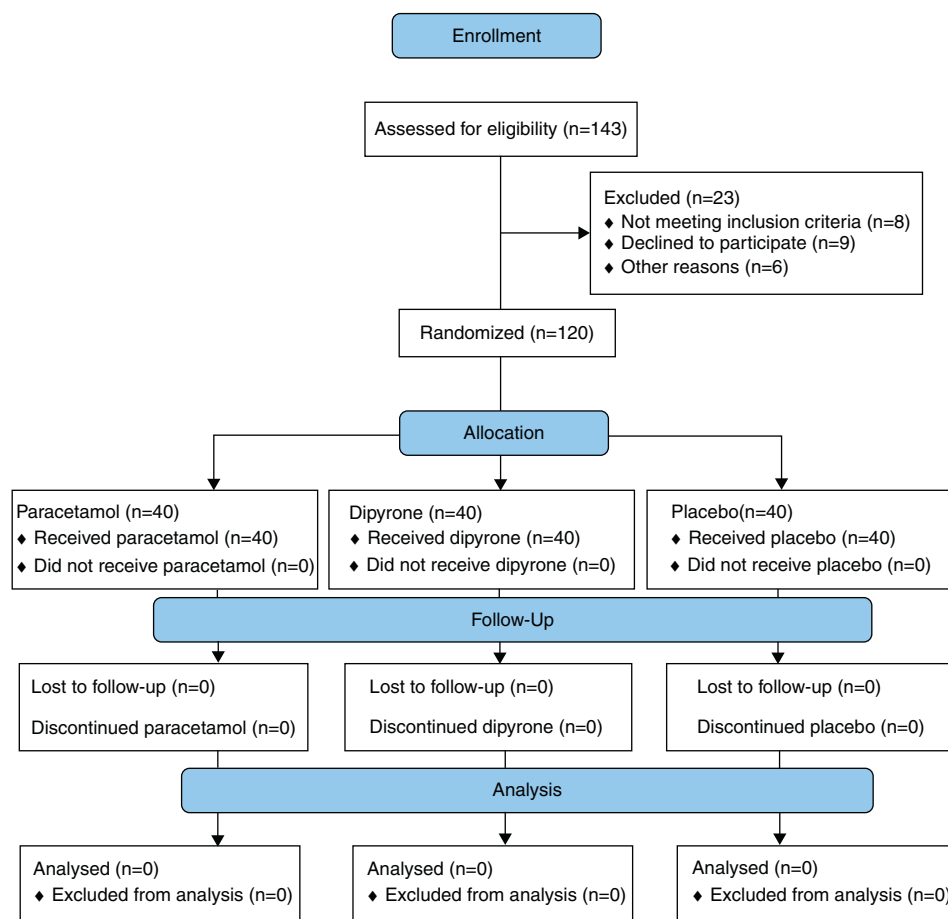


Figure 1 Enrolment process.

Table 1 Demographic and baseline clinical characteristics of the patients.

	Paracetamol (n = 40)	Dipyrrone (n = 40)	Placebo (n = 40)
Age (year)	9.4 ± 2.2	8.8 ± 2.2	9.2 ± 2.3
Weight (kg)	33.2 ± 12.9	30.6 ± 11.1	32.2 ± 12.3
Sex (male/female, n)	20/20	20/19	23/17
Duration of surgery (min)	39.1 ± 15.4	43.0 ± 13.0	37.3 ± 13.9

Values are means ± SD or numbers of patients, as appropriate.

Table 2 Mean pain scores (VAS) for each of the indicated times.

	Paracetamol (n = 40)	Dipyrrone (n = 40)	Placebo (n = 40)	p
VAS 30 min.	40.4 ± 30.6	39.8 ± 31.9 ^a	56.6 ± 27.2 ^a	0.044 ^a
VAS 1 h	16.8 ± 18.8	21.8 ± 11.1	24.1 ± 25.5	0.340
VAS 2 h	16.4 ± 15.0	28.1 ± 26.2	23.5 ± 25.3	0.173
VAS 4 h	18.3 ± 15.9	26.1 ± 28.5	26.1 ± 25.3	0.645
VAS 6 h	17.5 ± 15.8 ^b	20.9 ± 22.4 ^a	30.1 ± 23.3 ^{a,b}	0.045 ^a /0.013 ^b
VAS 12 h	19.6 ± 18.1	16.1 ± 15.4	24.5 ± 24.9	0.549
VAS 24 h	11.9 ± 11.7	11.2 ± 8.9	19.4 ± 19.1	0.244

Data are mean ± SD. VAS, visual analog scale (VAS values obtained from each group were compared with the other treatments at each time point using an analysis of variance).

^a $p < 0.05$, dipyrrone versus placebo.

^b $p < 0.05$, paracetamol versus placebo.

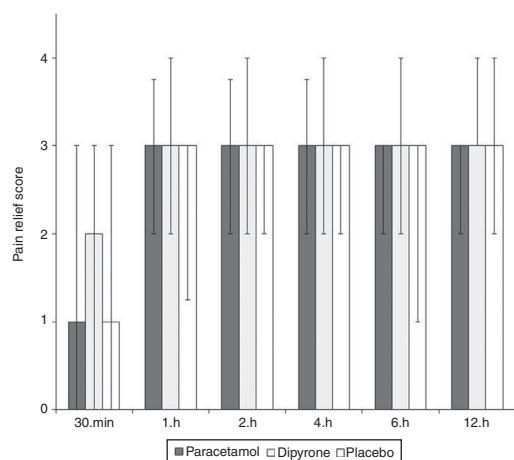


Figure 2 Pain relief scores of the patients in the groups during postoperative 24h.

The requirement for postoperative cumulative amounts of rescue analgesics for the paracetamol ($0.38 \pm 0.38 \text{ mg kg}^{-1} 24 \text{ h}^{-1}$) and dipyrone ($0.39 \pm 0.41 \text{ mg kg}^{-1} 24 \text{ h}^{-1}$) groups was significantly lower than those of the placebo group ($0.65 \pm 0.46 \text{ mg kg}^{-1} 24 \text{ h}^{-1}$) (paracetamol vs placebo, $p=0.013$; dipyrone vs placebo, $p=0.023$, Fig. 3). Fifteen patients (37.5%) in the paracetamol, 13 patients (32.5%) in the dipyrone, and 4 patients (10%) in the placebo group did not require rescue analgesics during the 24h after surgery. The amount of rescue analgesics for the paracetamol and dipyrone groups was significantly lower than those of the placebo group (paracetamol vs placebo, $p=0.004$; dipyrone vs placebo, $p=0.014$, Fig. 4).

The most frequent adverse effects were nausea (15.8%) and vomiting (29.2%) during the first 24h after surgery. No significant differences were found between groups with respect to nausea, vomiting and antiemetic medication

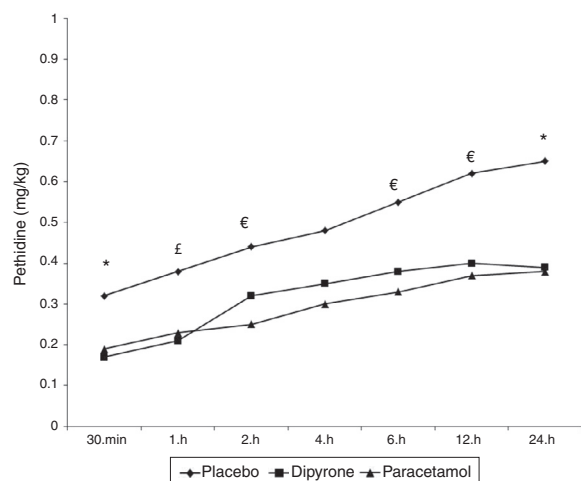


Figure 3 Total opioid requirements of the patient in the group during postoperative 24h. Values obtained from each group were compared with the other treatments at each time point via analysis of variance. * $P < 0.05$ paracetamol and dipyrone versus placebo. € $P < 0.05$ dipyrone versus placebo; £ $P < 0.05$ paracetamol versus placebo.

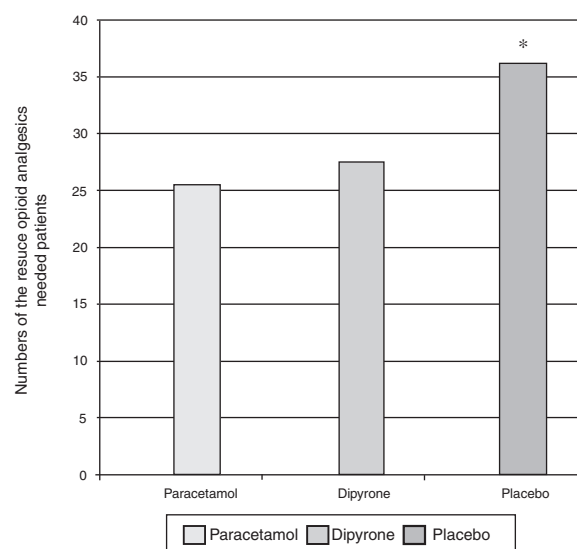


Figure 4 Rescue analgesics requirements of the patients in the groups during postoperative 24h.

($p > 0.05$, Fig. 5). Adverse effects including persistent nausea and vomiting, bleeding at the surgical field, dyspepsia, and allergic reactions were not recorded during the first 24h postoperatively. With respect to adverse effects, no significant difference was found among the groups studied ($p > 0.05$).

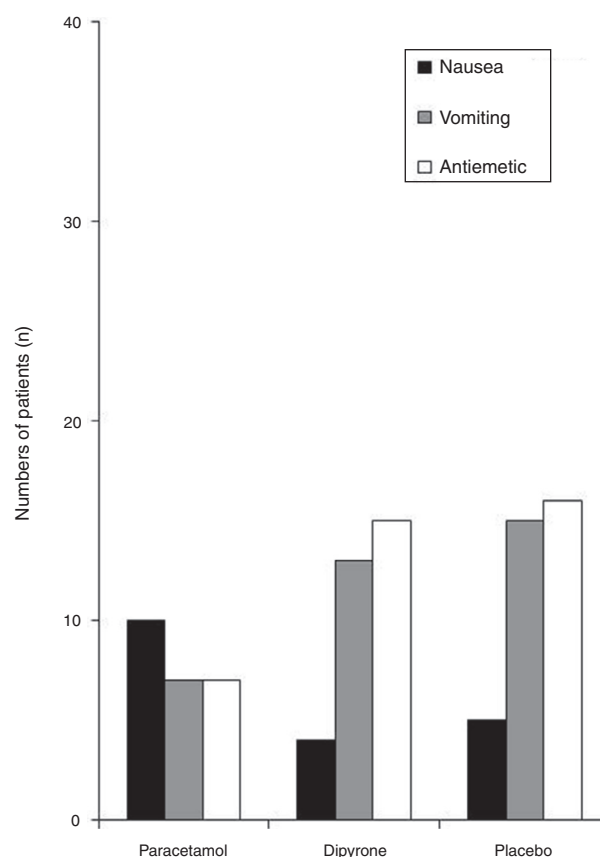


Figure 5 Incidence of nausea, vomiting and antiemetic medication in the study subjects during the first 24h after surgery.

Discussion

Our study revealed that the administration of paracetamol and dipyrrone by IV-PCA for the treatment of acute postoperative pain resulted in a well tolerability and had similar effective analgesic properties in children after tonsillectomy. The rescue opioid analgesic requirement during the first 24 h after surgery was significantly lower in the paracetamol and dipyrrone groups when compared with the placebo group.

IV-PCA is an effective method used for the treatment of postoperative pain in adults and children, while regulating the dose according to individual needs, and its use has expanded to even young children.^{2,14,15} In some of the studies,^{18–21} dipyrrone was successfully used in adults by IV-PCA for postoperative pain management. Although, IV paracetamol and dipyrrone are widely used in children, we have not encountered any report concerning paracetamol or dipyrrone use by IV-PCA for postoperative pain treatment for this group of age. Our study is the first prospective, randomized, double-blind, placebo-controlled study to compare IV-PCA with paracetamol and dipyrrone for postoperative pain management in children. Further studies may be warranted with various doses of paracetamol and dipyrrone to define the optimum IV-PCA regimen for postoperative pain management in children.

Why do practitioners administer IV non-opioids intermittently by bolus injection with hand-held injector for acute postoperative pain treatment in patients that already receives intra-operatively non-opioids intravenously and then continued every 6 h for 24 h? Markedly high and low levels of analgesic drugs may result as suboptimal management of postoperative pain with the intermittent IV bolus technique. We think that IV non-opioid analgesics should be administered by IV-PCA for acute postoperative pain treatment when appropriate. Non-opioid analgesics administered via IV-PCA should have well tolerability properties and low incidences of adverse effects. Paracetamol is a safe and well tolerated drug with minor adverse effects and proven efficacy when used perioperatively.^{22–24} IV paracetamol has significantly increased the use of perioperative analgesic.^{22–24} IV form of paracetamol seems to result in a better analgesic effect when compared with other forms.⁶ Dipyrrone is a widely used effective analgesic with low adverse effects.² In our study, adverse effects including persistent nausea and vomiting, bleeding at the surgical field, dyspepsia, and allergic reactions were not encountered during the first 24 h postoperatively. In addition to this, the incidence of nausea, vomiting and the need for antiemetic medication were similar in study drugs and placebo groups. In our study, we are surprised that there is no difference in the incidence of side effects in the placebo, paracetamol, and dipyrrone groups. Since the placebo group consumed significantly more pethidine than the other groups. We would have expected a lower incidence of nausea and vomiting in the two PCA groups since they consumed less pethidine. We think that the incidence of postoperative nausea and vomiting (PONV) is not only related to study medication but it is also related to the type of surgery as tonsillectomy. Paracetamol and dipyrrone are relatively well tolerated agents when compared with the other non-opioid analgesics with respect to potential side effects.^{25,26} We did not encounter

any complication related with paracetamol and dipyrrone without PONV. IV dipyrrone and paracetamol are commonly used non-opioid analgesics as the primary analgesic or adjunct to opioid analgesia for postoperative pain management in childhood in our country.

IV paracetamol and tramadol have similar analgesic properties after adenotonsillectomy in children.³ Dipyrrone and tramadol can be considered as alternative analgesics for treatment of postoperative pain when administered by IV-PCA.²⁰ IV dipyrrone has been revealed to be an effective analgesic^{6,18–21,27} and has equivalent efficacy to that of IV paracetamol for postoperative pain treatment.^{5,12} Korkmaz Dilmen et al.²⁸ demonstrated that IV paracetamol and dipyrrone provide effective analgesia after lumbar disk surgery when administered as rescue analgesic with morphine by PCA. On the other hand, Grundmann et al.²⁵ showed that dipyrrone is superior to paracetamol for acute postoperative pain treatment. However, their postoperative follow up period was limited to 2 h and was relatively short when compared with our study. In our study, pain scores in paracetamol and dipyrrone groups were low and similar over the course of the assessment period and the difference between the two groups with respect to rescue analgesic requirement was not significant. Our results suggest that administration of paracetamol and dipyrrone by IV-PCA are both effective and have similar analgesic properties for the treatment of acute postoperative pain following tonsillectomy in children.

PONV are frequent postoperative problems following general anesthesia especially after tonsillectomy. Use of opioid analgesic is an important factor in increasing risk of PONV. The risk of PONV depends on many other factors such as the patient, technique of the anesthesia, type of surgery, and medications administered.²⁹ In addition to this, swallowed blood and oropharyngeal irritation induce vomiting after tonsillectomy in children.³⁰ Adenotonsillectomy has the highest rate of PONV (54%) among the most commonly performed operations in children.³¹ Brodner et al.⁵ demonstrated that episodes of nausea and vomiting were not significant in the paracetamol and dipyrrone group when compared with placebo group after minor to intermediate surgery. They show that the incidence of side effects was not significant among the groups; the range of relative frequencies for nausea was between 30.6% and 42.9% and the range of relative frequencies for vomiting was between 18.4% and 24.5%.⁸ Uysal et al.³ showed that the frequency of nausea and vomiting are 22% and 19% respectively in IV paracetamol group after adenotonsillectomy in children. In our study, nausea developed in 15.8% patients and vomiting in 29.2%, but those were the only adverse effects experienced by our patients. Our results revealed findings similar to those of previous studies, and we think that the incidence of PONV is not only related to study medication but it is also related to the type of surgery.

In conclusion, both paracetamol and dipyrrone have good tolerability profile and have effective analgesic properties when administered by IV-PCA for postoperative analgesia after tonsillectomy in children.

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Conflicts of interest

The authors declare no conflicts of interest.

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